REMARKS

Applicant hereby requests further consideration of the application in view of the amendments above and the comments that follow. Claims 1-20 are pending in the application but stand rejected as will be discussed below. Claims 21-38 were previously restricted by the Examiner and canceled prior to submission of the Request for Continued Examination.

I. The Art Rejections over U.S. Patent No. 5,141,510 to Takagi et al. ("Takagi")

Claims 1-20 stand rejected as being anticipated by or, in the alternative, obvious over Takagi. The Action states that Takagi teaches a sintered tricalcium phosphate with tubes of diameter .1-2 mm, spherical pores of 50-60 micrometers, and a porosity of .5-40% (citing col. 2, lines 1-9 and Figures 1A-2). The Action also notes that Claims 3 is "generic" with respect to the phase of the final bone material. The Action concludes that the claims are "considered anticipated" or in the alternative "obvious" because of overlapping portion of the range disclosed in the prior art. Applicant disagrees.

Takagi proposes an artificial bone material for implantation as a substitution for bone. It is not resorbable. It is designed to substitute bone by providing an implantation material that remains in the body. The instant invention is not directed to artificial bone; rather, the instant invention provides material that promotes the formation of new bone, which is resorbed while promoting the formation of new bone. Clearly, resorbable bone augmentation material is distinctly different in material and physical properties from an artificial bone implant. As such, the claims are not anticipated by Takagi.

In addition, the process to produce the resorbable product and the resultant claimed structures are very different from those proposed by Takagi[1]. For example, Takagi proposes a high strength, high toughness material (col. 2, lines 33-36). The shape of the structure is produced by mixing a slurry of calcium phosphate powder with methylmethacrylate resin and animal (cat) hairs and pressing the slurry in a cold isotropic press to a shape. Takagi then

[1] Applicants also respectfully submit that at Claim 2 Takagi claims a porosity of the structure without specifying whether the percentage was with respect to weight, volume or density) which makes it difficult to assess the claimed feature. This is in contrast to the instant claims, which claim % porosity with respect to volume.

places hollow tubes at a separation distance to form a green body (believed to be formed by piercing tubular passages in a ceramic slurry). The green body is put in burning powder, sintered for about 1 hour, then machined to provide a pressure strength of 800 kgf/cm^2 (*see* Example, col. 5, lines 9-14).

It is also noted that, Takagi proposes hollowed minute tubes from a calcium phosphate arranged together in two-dimensional closely packed structures with spherical pores. In contrast, certain of the claims of the instant invention are directed to a sintered block form with interconnecting micropores of less than about 20 μm and are typically non-spherical (Figure 1) and can include tubular (typically drilled or milled) macropores.

In contrast, in certain embodiments, the shaped bodies of the instant invention can be produced by pressing calcium phosphate powder into blanks, milling or shaping the body into a desired shape and drilling or otherwise forming tubular holes in the shaped body. The drilling or forming of the tubular holes can be carried out so that the tubular pores are uniform.

Claim 1 recites:

> 1. Resorbable bone replacement and bone formation material based on porous β-tricalcium phosphate (β-TCP), produced by
>
> (a) baking a phosphate powder of a chemical composition having residue on baking which yields theoretically chemically pure tricalcium phosphate;
>
> (b) forming blanks having microporosity using the baked β-tricalcium phosphate (β-TCP); and
>
> (c) providing the baked blanks with substantially tubular pores,
>
> wherein
>
> the β-tricalcium phosphate (β-TCP) is baked at least twice and the formation of the thermodynamically stable adjacent phases of β-TCP is inhibited, wherein the method further comprises;
>
> (i) powdering a presynthesis product obtained according to step (a),
>
> (ii) optionally baking the powdered presynthesis product together with phosphate powder according to step (a) and powdering the material obtained and optionally repeating step (ii) at least once;
>
> (iii) compressing the powdered product obtained in step (i) or step (ii) to form the blanks of step (b) and subjecting the blanks formed to final ceramic baking; and
>
> (iv) subjecting the baked blanks, at least about 99.5% of which consists of pure β-tricalcium phosphate (β-TCP), to step (c), wherein the baked blanks are resorbable *in vivo*.

3. Resorbable bone replacement and bone formation material, produced by
(i) baking phosphate powder of a chemical composition having a residue on baking which yields theoretically chemically pure tricalcium phosphate as a presynthesis product, and powdering that presynthesis product;
(ii) baking the powdered presynthesis product and powdering the material obtained and optionally repeating step (ii) at least once;
(iii) compressing the powdered product obtained in step (ii) to form shaped blanks of resorbable β-tricalcium phosphate (β-TCP) having microporosity and subjecting the blanks formed to ceramic baking; and
(iv) providing the compressed baked blanks with substantially tubular macropores.

41. Resorbable bone formation material produced by:
pressing a baked body of sintered β-tricalcium phosphate (β-TCP) into a blank body of resorbable bone formation material having micropores;
shaping the blank body into a desired shape; then
drilling macropores having a substantially constant width over at least a major portion of a length thereof into the shaped body, the macropores extending through the shaped body in at least two different dimensions whereby some of the macropores cross over other of the macropores and also interconnect with micropores.

Takagi fails to teach or suggest at least the underlined recitations in the independent claims.

Still further, the structure proposed by Takagi is of hollowed tubes arranged in a single direction, in the direction of Haversian canals of bone. In contrast, certain embodiments include tubes arranged in 2 or 3 dimensions and configured at least partly in the direction of growth zone of bone. The tubes may be configured to provide interconnecting tubular macropores (*see, e.g.*, Claims 10, 41, and 45).

In summary, one of skill in the art would not find the claimed subject matter obvious in light of features found in a non-resorbable, solid, relatively high-strength artificial bone implant as proposed by Takagi. Indeed, placing macro (tubular) holes into a sintered body that is relatively frangible, and resorbable *in vivo*, is novel and very different from the structure proposed by Takagi. As such, Applicants submit that the claims are patentable over Takagi and request that this rejection be withdrawn.

II. The Art Rejections over U.S. Patent No. 6,340,648 to Imura et al. ("Imura") and U.S. Patent No. 6,511,510 to de Bruijn et al. (de Bruijn).

The Action rejects Claims 1-20 as being anticipated by and/or obvious over U.S. Patent No. 6,340,648 to Imura et al. ("Imura") and U.S. Patent No. 6,511,510 to de Bruijn et al. (de Bruijn). Applicants respectfully disagree.

The Action states that the terminology "generally tubular" and "substantially perpendicular" are considered "qualitative" and not considered to limit the claimed porosity to a specific structure. The Action states that it is not clear how the porosity must be generally tubular. Then, as the Action ignores the noted claim limitations, the Action states that absent "tangible evidence" to the contrary, the sintered articles are considered to possess the claimed particle diameter, as it is allegedly the Applicants burden to prove that the prior art composition does not posses the claimed composition characteristics. In particular, the Action inquires as to "how tubular" the porosity must be to be "generally" tubular.

First, Applicants submit that the terms "generally tubular" and "generally perpendicular" are not qualitative recitations and do positively claim the features of the macropores. Applicants submit that certain of the claims claim the shape of the macropores as tubular but that portions of the macropore may be formed so that the claimed macropore may have some shape variation along its length (such as at an intermediate segment or at an end portion where the shape may flare or converge). That is, a generally tubular macropore is a macropore that may have minor portions that are not tubular. For example, a macropore with a funnel shaped portion, irregular minor segments (such as a countersunk entry or exit portion), and the like. Further, Applicants submit that this terminology is clearly accepted patent claim language.

However, Applicants have amended the claims above in a non-narrowing manner to advance prosecution. In certain locations, an alternative term has been recited with respect to this feature, *i.e.*, that the macro pore has a substantially constant width over at least a major portion of a respective length thereof. In other locations, the claim terminology has been replaced with "substantially tubular" to also allow for coverage of macropore configurations that may vary from being tubular along its entire distance. Applicants submit that the alternate language covers at least the exemplary shapes noted above and the like.

Turning now to the cited art, for prosecution purposes only, Applicants will now argue

patentablity rather than priority over Imura, which has a priority date that is close to the instant application (Applicants reserve the right to argue priority in the future as may be necessary).

Applicants submit that Imura fails to teach or suggest, *inter alia*, a resorbable bone formation material and for at least this reason, similar to the discussion with respect to Takagi above, fails to anticipate or render the claimed subject matter obvious. Indeed, Applicants submit that Imura proposes a hydroxyapatite porous sintered body (col. 8, Example 1, lines 29-30, Example 2, lines 39-40, 60-61 and col. 9, Example 3, lines 4-6, 9-11, 19-20 and Example 4, lines 46-55). Hydroxyapatite is non-resorbable, and therefore is not a resorbable material as claimed. In addition, Imura fails to teach or suggest a resorbable material with elongate or tubular macropores (*see* independent Claims 48, 57, 75 and 83 and certain dependent claims).

Rather, Imura proposes "roughly spherical pores" (Claim 1) but no figures are provided so Applicants are not sure as to the meaning of this recitation. Also, Imura proposes a skeleton part (col. 5, lines 50-54).

Notably, Imura also produces its proposed non-resorbable material in a very different manner from that described in the pending application. The examples of Imura propose a foam slurry of water and calcium phosphate and organic additives. In contrast, embodiments of the instant invention produces the resorbable material by pressing, milling/drilling and heating as discussed above with respect to Takagi.

In addition, Applicants submit that the dependent claims also recite independently patentable subject matter, which is not taught or suggested by Imura (*see, e.g.,* the discussion below with respect to De Brujin). Imura is directed to "spherical pores" with statistical spherical porosity of 150μm pore diameter or more (col. 3, lines 66-67, col. 4, lines 1-5) and inter-pore communications of diameter 50μm or more. In contrast, in some embodiments, the mircopores of the instant invention may be non-spherical and/or have a width of about 20 μm or less and interconnect the macropores. In view of the foregoing, Applicants submit that the claims are patentable over Imura.

For the record, Applicants note that in light of the differences noted above, which are

not taught or suggested by Imura, Applicants have not analyzed the disclosure of Imura for other porosity, mechanical or structural differences as invited by the Action at p. 4, 2d paragraph.

The Action also states that the claims are rejected over De Brujin. However, De Brujin proposes an osteoinduction body of calcium phosphate, mainly hydroxyapatite (HA) with a content of between 10-12% by weight tricalcium phosphate. This material is so-called "biphasic calcium phosphate", a mixture of two different calcium phosphates. In contrast, embodiments of the instant invention are directed to pure-phase (typically about 95% or more by weight) tricalcium phosphate, which is substantially, if not totally, devoid of other calcium phosphates and HA. Further, the pore structures proposed by De Brujin are also different from that of the instant invention (compare, for example, Figures 5 and 6 of De Brujin and Figures 1 and 2 of the instant application).

De Brujin, similar to Imura, fails to teach or suggest at least tubular shaped macropores or macropores having a substantially constant width over at least a major portion of its length (independent Claims 1, 3, 39).

For at least the above reasons, Applicants respectfully submit that the claims are patentable over Imura and De Brujin and request that this rejection be withdrawn.

III. The Art Rejections over U.S. Patent No. 5,531,794 to Takagi et al. ("Takagi II")

The Action rejects Claims 1-20 as being anticipated by and/or obvious over U.S. Patent No. 5,531,794 to Takagi et al. ("Takagi II"). Applicants respectfully disagree.

Takagi II proposes a ceramic device for the promotion and formation of bone. However, the material stimulates the formation of bone but will remain in the defect. As such, and notably, the material proposed by Takagi II is not resorbable (*see, e.g.*, Example 5 discussing that there was no loosening of the prosthetic after 20 weeks). In contrast, as discussed above with respect to Tagaki, the instant invention is directed to resorbable bone replacement and formation material. The material of the instant invention will dissolve. Hence, as for Takagi discussed above, the materials of Takagi II and the instant invention are very different. As such, the claimed subject matter is patentable over the cited reference.

Applicants also submit that the method of producing the tubular passages is very different. Takagi II appears to propose forming the tubular passages by piercing a ceramic slurry which would appear to inhibit the formation of uniform pores (Claims 39, 40 and 43) and does not provide for forming tubular macropores that cross-over other macropores to provide an open interconnecting macroporous structure or other features recited in the pending claims.

Further, unlike certain of the pending claims, Takagi II proposes unidirectional parallel tubular pores, which do not cross over each other. The Action states that the tubular pores may be "perpendicular" (Action, p.4), citing col. 4, lines 1-10 of Takagi II. A closer look at the cited passage shows that the reference merely states that the tubular passages are arranged so that there is a center passage and peripheral passages that are located on the circle at an equi-angular distance, "i.e., in a cross section perpendicular to the length of the cylinder." Hence, the reference merely proposes unidirectional tubular passages arranged in circumferentially spaced apart arrangements relative to the length of the cylinder and does not teach or suggest macropores extending in different directions through the shaped body (so that at least one macropore can cross over another) as recited in some of the pending claims.

In view of the foregoing, Applicants submit that the pending claims are patentable over Takagi II.

IV. The Art Rejections over DE 3810803 to Heide et al. ("Heide")

The Action rejects Claims 1-20 as being anticipated by or obvious over Heide. The Action states that this reference teaches a synthetic bone material with a porous structure that has a $CaO:P_2O_5$ ratio of 3:1 calcium triphosphate (citing the abstract).

The Action opines that when a claimed composition "appears to be substantially the same as a composition disclosed in the prior art, the burden is properly on the applicant to prove by way of tangible evidence that the prior art composition does not necessarily possess characteristics attributed to the CLAIMED composition." However, this reference does not teach or suggest β-tricalcium phosphate (β-TCP) resorbable bodies as claimed. Indeed, the English abstract of this Heide reference (attached) states that the material is made by culturing

human bone cells outside the body. The synthetic bone material is produced by seeding human bone cells extracorporally on a porous substrate. As described by Heide, the porous substrate for the human cells can be made of biopolymers and calcium phosphate. Clearly, Heide proposes a very different method of making the material and a distinct material as that of the instant application. Applicants submit that Heide fails to teach or suggest, at least, a beta-phase resorbable bone formation material (Claim 1, 3, 41), purity (Claim 2), tubular macropores (Claims 1, 3, 41), particles of particular size (not phagocytable) (Claim 6), and the like.

In view of the foregoing, Applicants respectfully submit that the claimed subject matter is patentable over Heide.

V. The Provisional Double Patenting Rejection

The Action provisionally rejects the pending claims over Claims 1-87 of co-pending Patent Application No. [10/085,526], which is the serial number of the instant application. Applicants believe that the Examiner meant to refer to co-pending Patent Application Serial No. 10/930,965. The instant application and the related continuation application No. 10/930,965 are commonly owned (the assignee of record now being curasan AG). Applicants have submitted a Terminal Disclaimer to obviate the provisional rejection in the continuation application, which requires that any patent issuing therefrom be commonly owned with any patent issuing from this application. As such, a Terminal Disclaimer is not believed to be required for this application. However, if the Examiner disagrees, he is invited to contact the undersigned.

CONCLUSION

Accordingly, Applicants submit that the present application is in condition for allowance and the same is earnestly solicited. Should the Examiner have any matters outstanding of resolution, he is encouraged to telephone the undersigned at 919-854-1400 for expeditious handling.

Respectfully submitted,

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CERTIFICATION OF FACSIMILE TRANSMISSION UNDER 37 CFR 1.8

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Rosa Lee Brinson

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Database : GER
Patent Number : 03810803
Patent date: 1989-10-12
Title : USES UP ZUR MANUFACTURE OF A SYNTHETIC BONE MATERIAL WITH KOERPEREIGENEN QUALITIES
Inventor(s) : HEIDE, HELMUT, DR., 6233 KELKHEIM, DE JONES, DAVID, DR., 4400 MUENSTER, DE
Exemplary Claim(s) : 1. Procedure for the production of a synthetic bone material marked by body-own characteristics, by the fact that one human bone cells (Praeosteoblasten and Osteobla-sten) extrakorporal on that the natural bone mineral similar calciumphosphatischen materials, substrate materials in the form of bio polymers or mixturesfrom both breeds. 2. Procedure according to requirement 1, thus gekenn- it draws 45 that one as calciumphosphaetische materials the relationship CaOOs = 3: 1 as closely as possible corresponding calcium phosphates and as bio polymers kollagen uses. 3. Procedure according to requirements 1 to 2, ge thus-it marks 50 that one uses autologe bone cells. 4. Procedure according to requirements 1 to 2, by the fact characterized that one uses strange, but immunologically suitable patient coming of 55 bone cells. 5. Procedure according to requirements 1 to 4, by the fact characterized that one lets the cell cultures of the nutritive solution, deposited on the stencils, constantly flow around. 6. Procedure according to requirements 1 to 5, by the fact characterized that the matrix materials have a constant porous form. 7. Procedure according to requirements 1 to 6, by the fact characterized that the matrix materials in granu-it laerer form are present. 8. Procedure according to requirements 1 to 6, by the fact characterized that the porous matrix materials in I CD 4-CDW I O CD O o oo .....

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Format Examples

US Patent
US6024053 or 6024053

US Design Patent
D0318249

US Plant Patents
PP8901

US Reissue
RE35312

US SIR
H1523

US Patent Applications
20020012233

World Patents
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Patent Abstract

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GER 1989-10-12 03810803 **USES UP ZUR MANUFACTURE OF A SYNTHETIC BONE MATERIAL WITH KOERPEREIGENEN QUALITIES**

INVENTOR- HEIDE, HELMUT, DR., 6233 KELKHEIM, DE DE
INVENTOR- JONES, DAVID, DR., 4400 MUENSTER, DE DE

APPLICANT- BATTELLE-INSTITUT EV, 6000 FRANKFURT, DE DE
PATENT NUMBER- 03810803/DE-A1
PATENT APPLICATION NUMBER- 03810803
DATE FILED- 1988-03-30
DOCUMENT TYPE- A1, DOCUMENT LAID OPEN (FIRST PUBLICATION)
PUBLICATION DATE- 1989-10-12
INTERNATIONAL PATENT CLASS- A61L02700; C12N00500; A61L02712; A61L02738; A61L02746; C08L08906; C12N00500S; C12N00506B18
PATENT APPLICATION PRIORITY- 3810803, A
PRIORITY COUNTRY CODE- DE, Germany, Ged. Rep. of
PRIORITY DATE- 1988-03-30
FILING LANGUAGE- German
LANGUAGE- German NDN- 203-0222-6700-9

EXEMPLARY CLAIMS- 1. Procedure for the production of a synthetic bone material marked by body-own characteristics, by the fact that one human bone cells (Praeosteoblasten and Osteobla-sten) extrakorporal on that the natural bone mineral similar calciumphosphatischen materials, substrate materials in the form of bio polymers or mixturesfrom both breeds. 2. Procedure according to requirement 1, thus gekenn- it draws 45 that one as calciumphosphaetische materials the relationship CaOOs = 3: 1 as closely as possible corresponding calcium phosphates and as bio polymers kollagen uses. 3. Procedure according to requirements 1 to 2, ge thus-it marks 50 that one uses autologe bone cells. 4. Procedure according to requirements 1 to 2, by the fact characterized that one uses strange, but immunologically suitable patient coming of 55 bone cells. 5. Procedure according to requirements 1 to 4, by the fact characterized that

one lets the cell cultures of the nutritive solution, deposited on the stencils, constantly flow around. 6. Procedure according to requirements 1 to 5, by the fact characterized that the matrix materials have a constant porous form. 7. Procedure according to requirements 1 to 6, by the fact characterized that the matrix materials in granu-it laerer form are present. 8. Procedure according to requirements 1 to 6, by the fact characterized that the porous matrix materials in I CD 4-CDW I O CD O o oo

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